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### **Blood spot-based measures of glucose homeostasis and diabetes prevalence in a nationally representative population of young U.S. adults**

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#### **Abstract**

**Purpose—**We investigated under-studied, biomarker-based diabetes among young U.S. adults, traditionally characterized by low cardiovascular disease risk.

**Methods—**We examined 15,701 participants aged 24–32 years at Wave IV of the National Longitudinal Study of Adolescent Health (Add Health, 2008). The study used innovative and relatively non-invasive methods to collect capillary whole blood via finger prick at in-home examinations in all fifty states.

**Results—**Assays of dried blood spots produced reliable and accurate values of HbA1c. Reliability was lower for fasting glucose and lowest for random glucose. Mean (standard deviation) HbA1c was 5.6% (0.8%). More than a quarter (27.4%) had HbA1c-defined prediabetes. HbA1c was highest in the black, non-Hispanic race/ethnic group; inversely associated with education; and more common among the overweight/obese, and physically inactive. The prevalence of diabetes defined by previous diagnosis or use of anti-diabetic medication was 2.9%.

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Further incorporating HbA1c and glucose values, the prevalence increased to 6.8%, and among these participants, 38.9% had a previous diagnosis of diabetes (i.e., aware). Among those aware, 37.6% were treated and 64.0% were controlled (i.e.,  $HbA1c < 7\%$ ).

**Conclusions—**A contemporary cohort of young adults faces a historically high risk of diabetes but there is ample opportunity for early detection and intervention.

#### **Keywords**

HbA1c; Glucose; Diabetes Mellitus; Young Adult; Health Surveys; Dried Blood Spot Testing

In 2012, economic costs of diagnosed diabetes totaled \$245 billion, including \$176 billion in direct medical costs and \$69 billion in reduced productivity (1). The 2012 economic burden represents a 41% increase from \$174 billion in 2007. The largest components of medical expenditures for diabetes include hospital inpatient care (43%) and prescription medications for diabetes complications (18%). Type 2 diabetes onset at age 20 is associated with a 15 year reduction in life expectancy, increased risk of severe, chronic diabetes complications by age 40, and worse education attainment and employment outcomes (2, 3). As such, diabetes in the first few decades of life is clinically, economically and societally burdensome (3–6).

However, little is known about diabetes prevalence in contemporary populations of young adults in the United States, traditionally characterized by low cardiovascular disease risk. Given that 28% of the US population is unaware of their diabetes, exam-based assessments such as those from the National Health and Nutrition Examination Survey (NHANES) provide valuable information on the full burden of diabetes (7–10). Besides NHANES, to our knowledge, the National Longitudinal Study of Adolescent Health (Add Health) is the only other study from which it is possible to estimate biomarker-based prevalence of diabetes among contemporary U.S. young adults in their twenties.

Add Health—widely used in social, behavioral, and health science research (11)—is notable for its national probability sampling strategy, oversampling of typically underrepresented groups, and high response rate. Add Health is uniquely suited for examinations of the transition to adulthood. The larger sample of young adults (15–20 times the size of one NHANES cohort of young adults) enables potentially more precise estimates and comprehensive analysis of subgroup differences (e.g., incorporating finer racial/ethnic categorizations) (12–14). Additionally, the measurement of diabetes in field studies such as Add Health is distinct from and potentially more complicated than that in examination center-based studies, requiring adaptation of biomarker collection to more variable home environments and utilizing many more field staff.

In Add Health, measures of glucose homeostasis were obtained via an innovative and relatively non-invasive collection of capillary whole blood via finger prick. While these relatively recently developed methods of evaluating glucose homeostasis have been used in the Moving to Opportunity (MTO) housing experiment, Health and Retirement Study (HRS), National Social Life, Health, and Aging Project (NSHAP), and Los Angeles Family and Neighborhood Survey (LAFANS), little information is available on the validity and reliability of the measurements they generate (15–17). We therefore examined these

properties in the larger Add Health sample. Addressing gaps in the literature, the objectives of this study are to: first assess the quality of measures of glucose homeostasis derived from dried blood spot technology, and then to quantify diabetes prevalence overall and by important demographic, social, clinical and behavioral risk factors, thereby allowing assessments of health disparities.

#### **METHODS**

#### **Add Health study design and data collection**

Add Health enrolled a national probability sample of 20,745 U.S. adolescents in grades 7 through 12 during the 1994–1995 school year (Wave I response rate: 79%) (18). The Add Health cohort has been followed for over a 13-year period and represents over 22 million individuals. Three in-home follow-up interviews have been completed: Wave II in 1996 (88% of the eligible cohort at Wave I), Wave III in 2001–2002 (77%), and Wave IV in 2008 (80%). Each wave of the study was approved by the University of North Carolina Public Health-Nursing Institutional Review Board (Chapel Hill, NC).

Detailed information on Add Health's measures of glucose homeostasis has been published elsewhere (19). Briefly, all 15,701 Wave IV Add Health participants were asked whether a health care professional ever told them they had high blood sugar or diabetes (i.e., selfreported history of diabetes). Women were asked to exclude diagnoses during pregnancy. Anti-diabetic medication use within the preceding four weeks was inventoried by visually inspecting participant-assembled medication containers and categorizing their contents in real-time using Lexicon Plus™ (Lexi-Comp®, Inc.; Hudson, OH).

Capillary whole blood was collected via finger prick from voluntarily fasting (≥8 hours) and non-fasting participants onto seven-spot, Whatman 903® Protein Saver cards by trained and certified field interviewers, subjected to in situ desiccation, then shipped to FlexSite Diagnostics, Inc. (Palm City, FL) for assay of HbA1c (%), and to the University of Washington Department of Laboratory Medicine (Seattle, WA) for assay of glucose (mg/dl). The analytical sensitivity, within- and between-assay coefficients of variation were 3.0%, 2.2% and 2.4% for HbA1c and 22 mg/dl, 4.4%, and 4.8% for glucose. In paired whole blood and blood spots (n=80), HbA1c values were strongly associated (Pearson  $r = 0.99$ ). Associations in paired serum and blood spots (n=83) were equally strong for glucose concentrations (Pearson  $r = 0.97$ ).

**Test-retest reliability analysis in Add Health—**In a quality control study conducted over the course of field work, the short-term retest reliability of HbA1c and glucose was assessed in a race/ethnicity- and sex-stratified random sample of 100 Add Health Wave IV participants (mean age 29 years; 50% female; 64% non-Hispanic White; 16 % non-Hispanic Black; 12 % Hispanic/Latino; 8 % other) examined twice, one to two weeks (mean: 8.6 days) apart. At the two examinations, biospecimens were collected typically by the same field interviewer (84% of participants) and at approximately the same time of day (mean | difference|: 52 minutes; range 0–302 minutes).

The variance in measures of HbA1c (and separately, glucose) was partitioned in a random effects model by letting  $Y_{ii}$  be the measure on the i<sup>th</sup> participant at the j<sup>th</sup> visit:  $Y_{ii} = \mu$  $+P_i + m_j(i) + e_{ij}$ , where  $\mu$  is the sample mean and  $P_i$ ,  $m_j(i)$ , and  $e_{ij}$  are the normally distributed participant, measurement, and error effects with mean zero and variance  $\sigma_p^2$ ,  $\sigma_m^2$ , and  $\sigma_e^2$ , respectively. Assuming the variance components are independently distributed, the total variance of Y  $(\sigma_x^2)$  is:  $\sigma_x^2 = \sigma_p^2 + \sigma_m^2 + \sigma_e^2$ . Reliability was then estimated as the ratio of the between-participant to total variance:  $\sigma_p^2/\sigma_{T}^2$ , i.e. an intraclass correlation coefficient (ICC) with 95% confidence intervals estimated using the delta method (20). The ICC represents the proportion of variance not due to measurement variance. Random effects models were implemented in SAS® 9.1 using Proc Mixed and the restricted maximum likelihood method.

**Validity analysis in Add Health—**In a separate quality control study conducted over ten weeks of field work, a dried blood spot (DBS) from each of three donors was shipped twice weekly to FlexSite Diagnostics, Inc. ("Lab A") and assayed by laboratory staff masked to the origin of the samples. The 60 returned values of HbA1c were compared to values of HbA1c conventionally assayed in paired whole blood from the same donors on a G7 Automated HPLC-HbA1c Analyzer (Tosoh Bioscience, Inc., San Francisco, CA) by Duke University Health System Laboratories (Durham, NC) ("Lab B"). Accuracy was computed as the Lab A minus Lab B difference (bias, %) and its ratio with respect to the criterion standard (relative bias  $= 100 \times \text{bias/Lab B}$ ).

#### **Identification of diabetes and its medical management**

Diabetes was identified by incorporating self-reported history, anti-diabetic medication use, and abnormality of HbA1c and/or glucose identified by American Diabetes Association (ADA) diagnostic thresholds  $(21)$ : (1) HbA1c  $6.5 %$ , (2) non-fasting glucose  $200$  mg/dl, and/or (3) fasting glucose  $126 \text{ mg/dl}$ . Pre-diabetes (HbA1c = 5.7–6.4%) also was identified. Among those with diabetes, awareness was defined as reporting a previous diagnosis. Among those aware, treatment was defined as taking anti-diabetic medications and control of diabetes was defined as HbA1c <7%, according to ADA guidelines (22).

**Covariates—**Subgroups were defined by the following characteristics: sex (male, female), race/ethnicity (non-Hispanic whites, blacks, and Asian/Pacific Islanders, other race/ multiracial, Mexican-American, other Hispanic), education (0–11 years, high school graduate/GED, some college/Associate's degree, 4-year college) as well as foreign birth, insurance status, history of diabetes, use of anti-diabetic medication, and fasting  $\,8\,$  hours. Body mass index (BMI kg/m<sup>2</sup>) categories included: underweight/normal (<18.5–24.9); overweight  $(25.0-29.9)$ ; obese class I (30–34.9): obese class II/III ( $\overline{35.0}$ ). Central obesity was defined as waist circumference  $> 102$  cm (men) or  $> 88$  cm (women, excluding pregnant women) (23). Fast food intake was assessed via past-7 day frequency of eating from a fast food restaurant (0, 2 times, 3 times). Binge drinking was assessed via frequency of  $5$  (men) or  $4$  (women) drinks in a row (none, less than weekly, weekly). Cigarette smoking was assessed by past-30 day smoking frequency (none, less than daily, daily) (24–26). Moderate to vigorous recreational physical activity was defined as the

number of times in the past seven days participants engaged in various physical activities ( 5 times, 1–4 times, none) (27), assessed by summing responses to seven questions (e.g., "In the past seven days, how many times did you roller blade, roller skate, downhill ski, snow board, play racquet sports, or do aerobics?"). Measurement session was categorized as morning (8:30am), afternoon (1:30pm), and evening (5:30pm).

Analyses of HbA1c and glucose utilized data from 13,465 and 13,112 participants aged 24– 32 years with non-missing survey weights and assay results. Summary statistics were estimated using STATA®/SE 10 software (StataCorp LP, College Station, TX), accounting for the clustered design and using sample weights to adjust for unequal probability of selection and attrition, to produce nationally representative estimates.

#### **RESULTS**

In our analysis sample, the mean age of participants was 28 years and approximately half were female (Table 1). Two-thirds were white, with large proportions of blacks (14%) and Hispanics (11%). Results of our quality control studies suggest reliability was highest for HbA1c (ICC: 0.97), lower for fasting glucose (ICC: 0.66), and lowest for random glucose collected in the fasting or non-fasting state (ICC: 0.39) (Table 2). Within-participant coefficients of variation were 2.4% for HbA1c, 13.5% for fasting glucose, and 17.5% for random glucose (Table 2). HbA1c was over-estimated by an average of 0.2% in dried blood spot testing compared to conventional whole blood assays, but relative bias did not exceed 5% (Table 3).

The prevalence of HbA1c-defined diabetes was 3.6%. More than a quarter (27.4%) had HbA1c-defined pre-diabetes (Table 4). HbA1c was highest in the black, non-Hispanic race/ ethnic group; inversely associated with education; and more common among participants with a history of diabetes or elevated fasting glucose, users of anti-diabetic medication, the overweight/obese, and the physically inactive. Participants were not asked to fast, and only 16% fasted. Among fasters, racial/ethnic minorities, obesity, history of diabetes, and use of anti-diabetic medications were over-represented when compared to the entire population (not shown). Therefore prevalence of non-fasting glucose 200 mg/dl *or* fasting glucose 126 mg/dl was estimated: 2.5%, overall (Table 5). Discernible patterns of variation in glucose with participant characteristics reflected those of HbA1c, described above. Overall, 5.1% had either high HbA1c or high glucose (i.e., HbA1c  $\,$  6.5, fasting glucose  $\,$  126 mg/dl, or non-fasting glucose 200 mg/dl) and among these participants, only 24.0% reported a previous diagnosis of diabetes.

The prevalence of diabetes defined by previous diagnosis or use of anti-diabetic medication was 2.9% (95% CI: 2.5, 3.3) (Table 6). Further incorporating HbA1c and glucose values, the prevalence increased to 6.8%, and among these, 38.9% had a previous diagnosis of diabetes (i.e., aware). Among those aware, 37.6% were taking anti-diabetic medication (i.e., treated), and 64.0% had HbA1c < 7% (i.e., controlled).

Supplemental analyses compared diabetes prevalence in Add Health with similarly aged adults (24–32 years) in NHANES 2007–2008 (see Appendix A for details on NHANES

study design and cross-survey analyses). In NHANES, prevalence of diabetes incorporating self-reported history, anti-diabetic medication use, fasting glucose and HbA1c was 2.6% (n=294). Compared with NHANES, participants in Add Health were less likely to be foreign-born, uninsured, and have less than a high school education, and more likely to be obese (not shown). Between survey differences were attenuated after controlling for age, sex, race/ethnicity, foreign-birth, education, health insurance, BMI status, central obesity, fast food intake, physical activity, cigarette use, and heavy drinking; Add Health vs. NHANES adjusted risk ratio: 1.7 (95% CI: 0.8, 3.7).

#### **DISCUSSION**

We investigated the under-studied, biomarker-based prevalence of diabetes in a contemporary cohort of young U.S. adults by collecting capillary whole blood via finger prick and assaying HbA1c and glucose in dried blood spots (28). To put results in context, fasting plasma glucose has greater biological variability compared to HbA1c with coefficients of variation (CV) between 5–8% vs. 1–2%, respectively (29–31). Given biological variability, laboratory quality management standards designed to support informed medical decision-making suggest glucose analyses have desired analytic imprecision 2.3%, bias 1.8%, and total error 5.5% and that HbA1c (%) analyses have imprecision, bias and total error  $0.9\%$ , 1.5%, and 3.0%, respectively (32). In this study, we found that HbA1c values were highly reliable, minimally biased, and strongly correlated with fasting glucose. Analytic imprecision and bias of dried blood spot HbA1c approximated targeted analytic specifications derived from conventional clinical assays. Variability of glucose values from DBS slightly exceeded the range of previously reported estimates from conventional clinical analyses (33–35). However, glucose varied strikingly with participant characteristics related to well-known glucohomeostatic abnormalities, regardless of fasting status, and in doing so, mirrored blood spot-based HbA1c.

Next, we then turned to the identification of diabetes. The prevalence of HbA1c-defined prediabetes and diabetes was 27.4 and 3.6%. After incorporating history of diabetes, antidiabetic medications, high HbA1c, and high glucose, diabetes prevalence increased to 6.8%, with only 38.9% reporting a previous diagnosis of diabetes (i.e., aware). Among those aware, 37.6% were treated with medications and 64.0% were controlled.

#### **Study findings in context**

In recent decades, minorities and economically disadvantaged groups have experienced the greatest rise in diabetes and worst outcomes from this disease (36–39). Between-group disparities in diabetes among young adults align with those found for all U.S adults. Agestandardized diabetes prevalence is higher among non-Hispanic blacks, Hispanics, and those of other/mixed races compared to Asians and non-Hispanic whites. Diabetes is also inversely correlated with education and income (40).

Typically studies utilizing dried blood spots technology to identify diabetes are conducted among populations of older adults. For instance, in the 2006 Health and Retirement Study of adults over the age of 50, diabetes (HbA1c 6.5%) prevalence was 33% among blacks, 37% among Hispanics, and 17% among whites (41). Comparable prevalence estimates are

uncommon for younger U.S. adults at the forefront of the obesity epidemic. Moreover, diabetes is just one of many comorbidities that collectively foreshadow a future epidemic of chronic diseases among young people as they age (42–46). In Add Health among young adults, the prevalence of hypertension and obesity was 19% and 36%, respectively (47, 48).

#### **Study strengths and limitations**

In a nationally representative field study, we investigated the quality of measures of glucose homeostasis and the prevalence of diabetes among young U.S. adults, traditionally characterized by low chronic disease risk. The study used innovative, cost-efficient, and relatively non-invasive methods to collect capillary whole blood via finger prick at in-home examinations in all fifty states. Add Health's in-home collection of biomarkers at Wave IV enables researchers to study what appear to be rising rates of chronic diseases among younger-aged groups in the United States (44–47). Moreover, reliable estimates of disease can be produced in Add Health for many groups underrepresented in other surveys.

However, our study has some limitations. Attrition may be of concern. Females, whites, and those with higher SES had higher response rates at Wave IV. Nonetheless, non-response biases are small across diverse measures of demographic characteristics, health and risk behaviors (49). Moreover, non-response at Wave IV was neither associated with risk of prediabetes nor undiagnosed diabetes predicted from demographic characteristics, SES, health behaviors, and health status (unpublished results, Anna Bellatorre, University of Nebraska). Importantly, in our analyses, we utilized survey weights to adjust for attrition.

The lack of a fasting requirement in Add Health meant that fasting glucose was available for only a non-representative subset of participants. A random glucose cut-point of 200 mg/dl is endorsed by the ADA for diabetes diagnosis and widely used in cohort studies such as the Framingham Heart Study and ARIC study (22, 50–52). However, it may have lower sensitivity than other detection methods. For example, previous studies found that random glucose values ≥ 160 mg/dl had a sensitivity of 44% and specificity of 96% (8) compared to fasting glucose 120 mg/dl which had a sensitivity of 67% specificity of 98%, and HbA1c

≥ 6.3% which had sensitivity of 40% sensitivity and specificity of 98% (53). Some have proposed utilizing random glucose to enable cost-efficient opportunistic screening of diabetes (54, 55). A study of a large health care system found that 70% of patients had a measure of glycemia in the past 3 years and 95% of these measurements were random glucose—likely due to routine inclusion of random glucose in standard chemistry panels (56). Alternatively, in this study, reliability of HbA1c was excellent and prevalence of diabetes estimated by HbA1c ≥ 6.5% was available in both fasting and non-fasting populations. Advantages of HbA1c in identifying diabetes include convenience (no fasting requirement), greater pre-analytic stability, and ability to integrate exposure to hyperglycemia over the prior 2–3 months (57, 58). However, HbA1c may have lower sensitivity than fasting glucose (59, 60). Also, guidelines for identifying diabetes recommend basing diagnoses on repeat testing, an approach unavailable in this research study (21).

#### **Conclusions**

Diabetes is a growing problem in the United States with one study projecting that as many as one-third of adults could have diabetes in 2050 if trends persist (61). Low awareness of diabetes and the alarming rate of pre-diabetes among young adults suggest ample opportunity for early detection and intervention in a population often assumed to be unburdened by chronic conditions. National data from Add Health suggest that this cohort of young adults faces a historically high risk of cardiovascular disease, with higher than expected burden of diabetes as well as hypertension and obesity (47, 48). This finding is important because it may portend exponential growth in health issues and health care costs. Tackling disparities in the burden of chronic diseases, already apparent among young adults, is a critical endeavor.

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#### **List of abbreviations and acronyms**



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Characteristics of the Add Health Wave IV (2008) Participants Aged 24–32 years



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*a* Restricted to participants with HbA1c or glucose data

*b*<br>Percentages (95% confidence interval) weighted to be representative of U.S. adolescents in grades 7–12 during the 1994–1995 school year

 $c$ <br>
Abdominal obesity defined as  $> 102$  cm (men) and  $> 88$  cm (women, excluding pregnant women)



Reliability of HbA1c and Glucose, Add Health Wave IV (2008) Reliability of HbA1c and Glucose, Add Health Wave IV (2008)



 $c$ Within-participant coefficient of variation = 100\* (within-participant variation $1^{1/2}$ /mean)

<sup>C</sup>Within-participant coefficient of variation = 100<sup>\*</sup> (within-participant variation<sup>1/2</sup>/mean)

*d*<br>Among participants fasting ≥ 8 hours

 $d$  Among participants fasting  $\,$  8 hours

Comparing HbA1c values from dried blood spot testing to paired conventionally assayed whole blood, Add Health Wave IV (2008) Comparing HbA1c values from dried blood spot testing to paired conventionally assayed whole blood, Add Health Wave IV (2008)



ate overestimation *a*Bias = Dried blood spot value – conventionally assayed whole blood value; positive values indicate overestimation

 $b_{\text{Relative bias}} = 100 \times (\text{Bias/whole blood value})$  $b_{\rm Relative\ bias}$  = 100  $\times$  (Bias/whole blood value)

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Weighted to be representative of U.S. adolescents in grades 7-12 during the1994-1995 school year *a*Weighted to be representative of U.S. adolescents in grades 7–12 during the1994–1995 school year

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 $b$  Abdominal obesity defined as > 102 cm (men) and > 88 cm (women, excluding pregnant women) *b* Abdominal obesity defined as  $> 102$  cm (men) and  $> 88$  cm (women, excluding pregnant women)

#### High Glucose (mg/dL) Prevalence by Participant Characteristics





 $a$ <sup>a</sup>Weighted to be representative of U.S. adolescents in grades  $7-12$  during the 1994–1995 school year

*b* Abdominal obesity defined as > 102 cm (men) and > 88 cm (women, excluding pregnant women)

#### Diabetes and Its Medical Management



Missingness varies due to availability of variables used to define diabetes

 $a$ Weighted to be representative of U.S. adolescents in grades  $7-12$  during the 1994–1995 school year

*b* Anti-diabetic medication use

*c* History of being told by a doctor or healthcare professional that you have diabetes (if female, outside of pregnancy).

*d*<br>For HbA1c, non-fasting glucose, and fasting glucose: 6.5%, 200 mg/dl and 126 mg/dl, respectively